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WAYS THAT FOODS CAN AFFECT THE BRAIN

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The mechanism by which brain neurons send signals to other cells involves the release of particular chemicals, neurotransmitters, that are produced in and released from each neuron's myriad terminals. About 30 or 40 compounds have been identified that seem to function as neurotransmitters somewhere in the brain. In general, each of these compounds can be released from many distinct groups of brain neurons which are distinguished by the locations of their cell bodies and terminals, and which subserve different functions. It appears that the rates at which some of the neurotransmitters are synthesized, and the quantities of them that are released, normally vary in nonmalnourished individuals, depending upon the composition of the food that has most recently been eaten. These changes in neurotransmitter release can also be associated with functional and behavioral consequences, thereby allowing one's nutritional state to affect one's behavior. This paper discusses the particular transmitters that are nutrient-dependent; the processes that couple food consumption to neurotransmitter synthesis; and some of the consequences of this coupling.

Nutritional Control of Serotonin Synthesis

The synthesis of serotonin, 5-hydroxytryptamine (5-HT), in neurons is initiated by the hydroxylation of the essential amino acid tryptophan. The enzyme that catalyzes this reaction, tryptophan hydroxylase, has a poor affinity for its amino acid substrate. Hence, treatments that raise or lower brain tryptophan levels can, by changing the enzyme's substrate saturation, rapidly alter the rate at which tryptophan is hydroxylated and the rate at which its product (5-hydroxytryptophan) is converted to serotonin.[1] Brain tryptophan levels in rats, and probably in human beings, normally undergo pronounced variations when plasma amino acid patterns change, for example, when foods are being digested and absorbed. A high-carbohydrate, protein-poor meal elevates brain tryptophan, accelerating serotonin synthesis.[2] In contrast, a high-protein meal depresses serotonin synthesis.[3] The plasma parameter that couples food composition to brain tryptophan level is the ratio of the plasma tryptophan concentration to the summed concentrations of such other large neutral amino acids (LNAA) as tyrosine, phenylalanine, and the branched-chain amino acids leucine, isoleucine and valine.[3-6] This parameter is important because the transport macromolecules (within the capillary endothelia comprising the blood-brain barrier) that carry circulating tryptophan into the brain also transport the other LNAA with almost equal efficiency, so circulating tryptophan must compete with the other LNAA for transport sites.[7] A carbohydrate-rich meal raises the plasma tryptophan ratio[8] by eliciting the secretion of insulin, which has little effect on plasma tryptophan but greatly lowers plasma levels of the other LNAA, largely by facilitating their uptake into skeletal muscle. A protein-rich meal depresses the ratio by contributing very large quantities of the branched-chain amino acids to the systemic circulation but only small amounts of tryptophan (which is the least abundant amino acid in proteins and also is

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destroyed in the liver). This coupling of food composition to serotonin release allows serotoninergic neurons to function as variable ratio sensors, informing the rest of the brain about the proportions of protein and carbohydrate in the most recent meal or snack. The brain can then use this information in deciding what to eat at the next meal or snack.

Serotonin release from brain neurons can also be increased by ingesting pure tryptophan, especially by taking it along with an insulin-releasing carbohydrate (to lower the levels of the other plasma LNAA, thereby facilitating tryptophan's uptake into the brain).[9] Conversely, serotonin release can be depressed by ingesting large doses of any other LNAA, including both the amino acids that are naturally present in protein and synthetic compounds, like L-dopa or α-methyldopa, which are used therapeutically.[10] Tryptophan's efficacy — and that of any other natural or synthetic LNAA — is diminished if it is consumed along with protein; the LNAA in the protein suppress its uptake into the brain.

Brain Serotonin and Appetite Control

If animals are allowed to choose concurrently from among two or more diets (unfortunately an unusual circumstance in most research on appetite control) each containing different proportions of carbohydrates or protein or both, their behavior indicates that they are able to regulate not only the total quantities of food and of calories that they consume, but also the proportions of protein[11] and carbohydrates.[12] Administration of a small carbohydrate-rich pre-meal before exposure to the test diets[13] or administration of drugs (e.g., D-fenfluramine or fluoxetine[14]) that enhance serotonin's release or suppress its inactivation causes the animal to adjust its food choices so as to increase the proportion of protein to carbohydrate in the next meal. Similar observations have been made in people given D-fenfluramine (or, to a lesser extent, tryptophan) and allowed to choose among snacks[15] or meal constituents containing varying proportions of protein and carbohydrate. All who responded to D-fenfluramine by reducing total calorie intake also significantly decreased the proportion of calorie intake supplied by carbohydrate and increased the proportion supplied by protein. Fat consumption was not significantly affected. Most of the decline in carbohydrate intake in such experiments is related to reduced consumption of snack foods[16] and not of meal-time carbohydrates. These observations imply that the brain mechanisms regulating protein and carbohydrate appetites involve, among others, serotonin-releasing neurons. A carbohydrate-rich, protein-poor meal that increases brain serotonin levels reduces the likelihood that the next meal will be of similar composition. Conversely, consumption of carbohydrate-poor, protein-rich meals (like those often used for weight reduction) diminishes brain serotonin synthesis and sometimes increases the subject's desire for carbohydrate to the point of carbohydrate-craving.[17] Prolonged consumption of such meals may exacerbate the lowering of brain serotonin and the carbohydrate craving by diminishing the quantities of insulin secreted after meals. This would be expected to further increase plasma levels of the competing branched-chain LNAA. If an obese subject also happened to be insulin-resistant, this might further raise plasma LNAA and depress brain serotonin release.

We observe that a sizable proportion of obese subjects seeking assistance in weight reduction consume as much as half of their total daily intake as carbohydrate-rich snacks, and that this behavior is often associated with strong feelings of carbohydrate craving. Conceivably, this appetite disorder reflects an abnormality in the process that couples carbohydrate consumption to the release of brain serotonin. Many patients describe themselves as feeling anxious, tense or depressed before consuming the carbohydrate snack and peaceful or relaxed afterwards. It may be more than a coincidence that dietary carbohydrates and both major classes of antidepressant drugs, the monoamine-oxidase inhibitors and the tricyclic-uptake blockers, are thought to increase the quantities of serotonin present within brain synapses. Perhaps the subjects snacking on carbohydrates are unknowingly self-medicating.

Carbohydrate consumption or tryptophan administration can also modulate other normal behaviors, increasing subjective fatigue and

sleepiness, accelerating sleep onset in people with prolonged sleep latencies,[18] diminishing sensitivity to mild pain, and (in people over 40) increasing the likelihood of errors in performance tests.[19] At present, no information is available on the relative potencies of sugars and starches in producing such effects. It might be expected that a carbohydrate's potency would depend upon its speed of absorption and its ability to stimulate insulin secretion.

Nutrients and Control of the Synthesis of Catecholamines and Acetylcholine

The rates at which the enzymes tyrosine hydroxylase and choline acetyltransferase convert tyrosine to dopa[20,21] and choline to acetylcholine,[22,23] respectively, can be modulated by treatments that change brain levels of tyrosine or choline. Brain tyrosine levels are most conveniently increased by ingesting pure tyrosine alone or with a carbohydrate (to lower plasma levels of the competing LNAA). Consumption of a high-protein meal also increases the plasma tyrosine ratio and brain tyrosine levels slightly, but probably not enough to have major effects on catecholamine synthesis. Brain choline levels are increased by consumption of pure choline or of phosphatidylcholine (lecithin),[24] the substance providing most of the choline in the diet. Choline uptake into the brain is also catalyzed by a transport macromolecule within the endothelia of brain capillaries;[7] apparently, choline is the only important circulating ligand for this transport mechanism.

Under basal conditions, when a particular catecholaminergic or cholinergic neuron is not firing frequently, it will respond poorly if at all to an increase in available tyrosine[25,26] or choline.[27] However, when the neurons are physiologically active, they concurrently become highly responsive to increases in precursor levels, synthesizing and releasing more dopamine, for example, when brain tyrosine levels are raised[6,28] and more acetylcholine after choline[29] or lecithin[30] is eaten. The biochemical mechanism that couples neuronal firing frequency to tyrosine-responsiveness apparently involves the activation (by phosphorylation) of tyrosine hydroxylase. This process greatly increases the enzyme's affinity for, and saturation with, its tetrahydrobiopterin cofactor, causing its activity to become limited by the extent to which it is saturated with its amino acid substrate, tyrosine.[31] Phosphorylation of the enzyme also diminishes its sensitivity to end-product inhibition by catecholamine, further increasing the rate at which the neuron converts tyrosine to dopamine or noradrenaline. The biochemical mechanism that couples a cholinergic neuron's firing frequency to its ability to synthesize more acetylcholine when given more choline remains unknown.

The fact that catecholaminergic and cholinergic neurons must be exhibiting sustained physiological activity in order to display precursor-responsiveness (a relationship that is not typical of serotoninergic neurons[32]) imparts considerable specificity to the functional consequences of giving patients tyrosine or choline. The brain apparently can choose which particular catecholaminergic or cholinergic neurons will be allowed to respond to having more precursor simply by doing what brains normally do, i.e., modulating the firing frequencies of each group of neurons that releases these transmitters. This ability probably explains the paucity of side effects observed when people are given even very large doses of tyrosine[33,34] or of choline-containing compounds.[35,36] It also explains why a particular dose of tyrosine can be used either to *reduce* blood pressure in hypertension[37] (by enhancing noradrenaline release from the brainstem noradrenergic neurons that reduce sympathetic outflow) or to *raise* blood pressure in hemorrhagic shock[38] (by increasing catecholamine secretion from the physiologically active sympathoadrenal cells).

Attempts to use tyrosine or choline-containing compounds to treat diseases of catecholamine or acetylcholine deficiency are in their infancy. Progress has been retarded by the unusual regulatory status of these compounds (foods or drugs?) and by the unavailability, until recently, of pure and palatable lecithin preparations. Tyrosine has been reported to help some patients with depression[39] or mild Parkinson's disease.[34] Choline or lecithin have been used successfully to treat tardive dyskinesia,[35,40,41] mania[42] and ataxias.[36] Administration of choline or lecithin alone for short

periods has not led to reproducible improvement in patients with advanced Alzheimer's disease.[43] However, administration of high doses of nearly pure lecithin for longer periods (20 to 25 g daily for 6 months) apparently improved learning-memory and self-care indices in older patients who had a milder form of the disease.*

Summary

Numerous food constituents can affect the synthesis of brain neurotransmitters, and thereby modify brain functions mediated by the transmitters. This article describes the effects of dietary carbohydrate or protein on brain serotonin synthesis, and the involvement of serotonin-releasing neurons in control of appetite. Finally, it also mentions the changes in brain acetylcholine or catecholamine levels that can be induced by giving a dietary choline source or pure tyrosine. □

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